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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,464	NIEHRS ET AL.	
	Examiner	Art Unit	
	JON M. LOCKARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 10-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9 and 16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-25* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II, claims 8 and 9, drawn to a method for identifying a binding partner for Kremen, in the reply filed on 10 September 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-7 and 10-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10 September 2007. With regard to the further restriction requirement, Applicant's election with traverse of the combination of Kremen 1 and Kremen 2, in the reply filed 31 December 2007 is also acknowledged. Applicant argues at pg 7 of the response (filed 10 September 2007) that Kremen 1 and Kremen 2 are not independent and distinct in the context of the elected method. Applicant further argues at pg 7-8 of the response that Kremen 1 and Kremen 2 are highly homologous proteins, and thus an examination of both together would not represent an additional burden on the Examiner. Lastly, Applicant argues at pg 8 of the response that the reference cited to break unity of the invention does not anticipate the single general inventive concept of the elected group of invention. Applicant's arguments have been fully considered but are not found persuasive for the following reasons. With regard to the arguments that Kremen 1 and Kremen 2 are not independent and distinct, and a search of both would not represent an additional burden on the examiner, it is noted this application is a national stage application and therefore U.S. restriction practice (i.e.,

independent/distinct, undue search burden) does not apply. The individual polypeptides do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Each polypeptide represents a structurally and functionally different chemical compound from each other, which can be made and used without the other compounds. Lack of unity is shown because these compounds lack a common utility which is based upon a common structural feature which has been identified as the basis for that common utility. Furthermore, it is noted that the Nakamura et al. reference was used to break unity of invention of the claimed inventions, not the elected invention.

2. The restriction requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

3. The response filed 10 September 2007 has been received and entered in full. Claims 1-7 and 10-15 have been withdrawn without prejudice. Newly added claims 16-25 will be examined as they fit under the rubric of the elected invention. Therefore, claims 1-25 are pending, and claims 8-9 and 16-25 are the subject of this Office action. It is noted that the elected invention is the combination of Kremen 1 and Kremen 2, and the claims have been examined to the extent that they read upon the elected invention.

Drawings

4. Figure 5 is objected to because 37 CFR 1.84 states that "[P]artial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by

a *capital* letter". In the instant case, Figures 5 has two panels which should be labeled Fig. 5A and Fig. 5B and be referred to as such in the Brief Description of the Figures.

5. Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should *not* be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 09 February 2005 has been considered by the examiner.

Specification

7. The disclosure is objected to because of the following informalities:

8. The title of the invention is not descriptive. A new title is required that is clearly

indicative of the invention to which the claims are directed.

Claim Objections

9. Claims 8, 9, 16, 19, 21, and 24 are objected to because of the following informalities. Claims 8, 9, 16, 19, 21, and 24 encompass non-elected inventions, e.g., Kremen 1 *or* Kremen 2. Appropriate correction is suggested.

Claim Rejections - 35 USC § 112, 1st Paragraph (Enablement)

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 8-9 and 16-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the *enablement* requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

12. Claims 8-9 and 16-25 are drawn to a method for identifying a compound for modulating the Wnt signal cascade which is based on identifying a binding partner to a Kremen 1 and Kremen 2 polypeptide comprising determining whether the compound an activity of said polypeptide or whether binding of the compound to said polypeptide has occurred. The claims also recite a method for identifying a compound for modulating the Wnt signal cascade as an activator/agonist or inhibitor/antagonist of a Kremen 1 and Kremen 2 polypeptide comprising

assaying a biological activity. The claims also recite wherein the compound to be screened is an antibody that recognizes Kremen 1 and Kremen 2, a small molecule, or nucleic acid, and wherein the method is carried out using cell-free preparations or utilizes cells which express Kremen 1 and Kremen 2. However, the instant specification fails to teach how to achieve the proposed method, thus requiring undue experimentation of one skilled in the art to use the claimed invention with a reasonable expectation of success.

13. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

14. Claims 8-9 and 16-25 are drawn to a method for identifying a compound for modulating the Wnt signal cascade which is based on identifying a binding partner to a Kremen 1 and Kremen 2 polypeptide, which the specification teaches includes polypeptides with as little as 40% sequence identity to the Kremen 1 and Kremen 2 polypeptides shown in Figure 2 (See pg 6, 2nd paragraph. The claims also recite a method for identifying a compound for modulating the Wnt signal cascade as an activator/agonist or inhibitor/antagonist of a Kremen 1 and Kremen 2 polypeptide. The claims also recite wherein the compound to be screened is an antibody that recognizes Kremen 1 and Kremen 2, a small molecule, or nucleic acid, and wherein the method is carried out using cell-free preparations or utilizes cells which express Kremen 1 and Kremen 2. However, based on the low degree of sequence identity between the Kremen1 and Kremen2

polypeptides (32% sequence identity between mouse Kremen 1 and mouse Kremen 2, for example), one skilled in the art would not expect that a compound which binds to Kremen 1 would also bind to Kremen 2, or that a compounds which modulates (either activates or inhibits) the activity of the Kremen1 polypeptide would also modulate the activity of the Kremen2 polypeptide. Even if *arguendo* the claimed methods could be used to identify compounds which bind to both Kremen 1 and Kremen 2, one skilled in the art would not be able to predict, with any level of certainty, whether or not a compound that bound to Kremen 1 and Kremen 2 would actually modulate Kremen 1 and Kremen 2 activity, and thus modulate the Wnt signal cascade. Without some measure of Kremen 1 and Kremen 2 activity, one skilled in the art would not expect that every compound that bound Kremen 1 and Kremen 2 would modulate the Wnt cascade, either via direct inhibition or activation of the receptor, or indirectly via interfering with ligand binding.

15. The art recognizes that the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem

and Tertiary Structure Prediction, pp. 492-495). Even if an active or binding site were identified in the specification, that may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution or deletion of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2).

16. Furthermore, claims 8-9 and 16-25 are drawn quite broadly to a method for identifying a compound for modulating the Wnt signal cascade which is based on identifying a binding partner to a Kremen 1 and Kremen 2 polypeptide, which the specification teaches includes polypeptides with as little as 40% sequence identity to the Kremen 1 and Kremen 2 polypeptides shown in Figure 2 (See pg 6, 2nd paragraph). The claims also recite a method for identifying a compound for modulating the Wnt signal cascade as an activator/agonist or inhibitor/antagonist of a Kremen 1 and Kremen 2 polypeptide. The claims also recite wherein the compound to be screened is an antibody that recognizes Kremen 1 and Kremen 2, a small molecule, or nucleic acid, and wherein the method is carried out using cell-free preparations or utilizes cells which express Kremen 1 and Kremen 2. While the specification provides adequate guidance for the skilled artisan to make and use the Kremen 1 polypeptide of SEQ ID NOs:5-6 (mouse and human, respectively) and the Kremen 2 polypeptide of SEQ ID NOs:7-8 (mouse and human, respectively) in the claimed methods, it does not provide adequate guidance for a commensurate number of the claimed species of Kremen 1 and Kremen 2 polypeptides, which the specification

teaches includes polypeptides with as little as 40% sequence identity to the Kremen 1 and Kremen 2 polypeptides shown in Figure 2 (See pg 6, 2nd paragraph). Furthermore, neither the instant specification nor the art of record teach any variants of the Kremen 1 or Kremen 2 polypeptides that can modulate the Wnt signal cascade. Other than the polypeptides of SEQ ID NOs:5-8, the disclosure fails to provide sufficient guidance and information regarding the structural and functional requirements commensurate in scope with what is encompassed by the instant claims. Based on the very limited number of disclosed species of Kremen 1 and Kremen 2 polypeptides, the disclosure fails to provide sufficient guidance and information regarding the structural and functional requirements commensurate in scope with what is encompassed by the instant claims, and it would require undue experimentation to determine such. As set forth above, the state of the art is such that the relationship between the sequence of a protein and its activity is not well understood and unpredictable, and that certain positions in the sequence are critical to the protein's structure/function relationship and can only tolerate only relatively conservative substitutions or no substitutions. As the specification does not teach how to make and use a number of species that would be commensurate in scope with the claims, one skilled in the art would require undue experimentation to practice the invention in a manner commensurate in scope with the claims, given the lack of guidance in the specification and the very broad scope of the claims.

17. Moreover, claims 8, 9, 16-18, 20-23, and 25 are drawn to a method for identifying a compound for modulating the Wnt signal cascade which is based on identifying a binding partner to a Kremen 1 and Kremen 2 polypeptide comprising determining whether the compound an

activity of said polypeptide or whether binding of the compound to said polypeptide has occurred. The claims also recite a method for identifying a compound for modulating the Wnt signal cascade as an activator/agonist or inhibitor/antagonist of a Kremen 1 and Kremen 2 polypeptide comprising the steps of: (a) incubating a candidate compound with said polypeptide; (b) assaying a biological activity, and (c) determining if a biological activity of said polypeptide has been altered. The claims also recite wherein the compound to be screened is an antibody that recognizes Kremen 1 and Kremen 2, a small molecule, or nucleic acid, and wherein the method is carried out using cell-free preparations. However, the specification does not provide any direction or guidance or working examples of how to assess Kremen 1 or Kremen 2 polypeptide activity in a cell-free system, thus one skilled in the art would not know how to practice the claimed method without undue experimentation.

18. Due to the large quantity of experimentation necessary to generate the infinite number of Kremen 1 and Kremen 2 variants and derivatives encompassed by the claims; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide binding/activity of the Kremen 1 and Kremen 2 variants and derivatives; the breadth of the claims which fail to recite any structural or functional limitations for the Kremen 1 and Kremen 2 polypeptides; the lack of direction/guidance presented in the specification regarding how to assess polypeptide activity in a cell-free system and the absence of working examples directed to the same; and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure, function, and binding properties; undue

experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, 1st Paragraph (Written Description)

19. Claims 8-9 and 16-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. The claims are drawn quite broadly to a method for identifying a compound for modulating the Wnt signal cascade which is based on identifying a binding partner to a Kremen 1 and Kremen 2 polypeptide. The claims also recite a method for identifying a compound for modulating the Wnt signal cascade as an activator/agonist or inhibitor/antagonist of a Kremen 1 and Kremen 2 polypeptide. The claims also recite wherein the compound to be screened is an antibody that recognizes Kremen 1 and Kremen 2, a small molecule, or nucleic acid, and wherein the method is carried out using cell-free preparations or utilizes cells which express Kremen 1 and Kremen 2. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claims is the recitation of a name, i.e., Kremen 1 and Kremen 2 polypeptide, which the

specification teaches includes polypeptides with as little as 40% sequence identity to the Kremen 1 and Kremen 2 polypeptides shown in Figure 2 (See pg 6, 2nd paragraph). There is not even identification of any particular portion of the structure that must be conserved.

21. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of two species of Kremen 1 polypeptide (SEQ ID NOs:5-6) and two species of Kremen 2 polypeptide (SEQ ID NOs:7-8) is not adequate written description of an entire genus of functionally equivalent polypeptides, which incorporate all variants, derivatives, and homologs encompassed by the claims.

22. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

23. With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

25. Therefore, only a Kremen 1 polypeptide comprising the amino acid sequence SEQ ID NO:5 or SEQ ID NO:6, and a Kremen 2 polypeptide comprising the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:8, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 2nd Paragraph

26. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

27. Claims 8-9 and 16-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

28. Claim 8 recites the limitation "contacting said polypeptide" in 4 of the claim, and claim 9 recited the limitation "incubating a candidate compound with said polypeptide. There is insufficient antecedent basis for these limitations in the claims. Since claim 8 and 9 recite Kremen 1 and Kremen 2, it is unclear what polypeptide the limitation is referring to.

29. Claim 8 is rejected as being indefinite because it is unclear what is meant by the phrase "whether the compound an activity of said polypeptide". Since the term "effects" has been lined through, it is unclear what is encompassed by the claim.

30. Claims 16-25 are rejected for depending from an indefinite claim.

Summary

31. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Manjunath N. Rao, Ph.D.**, can be reached on **(571) 272-0939**. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jon M. Lockard, Ph.D.
April 12, 2008

/Jon M Lockard/
Examiner, Art Unit 1647